REMARKS

Status of the Claims

Claims 101-130 were pending in this application.

Claims 101-130 stand rejected.

Claims 101, 102, 103, 104, 111, 117, 126 and 127 are amended.

Claim 112 is canceled.

Reconsideration is respectfully requested.

It is gratefully acknowledged that the rejection stated in the Office Action of November 17, 2004, under Section 112, first paragraph, has been withdrawn.

Response to Office Action

Rejections under Section 102

Claims 101, 105-111, 113-116, and 126-130, stand rejected under Section 102(e) in view of US Pat. 6,867,305 to Danishefksy, *et al.* (hereinafter '305 or "the '305 patent").

It is argued that the '305 patent anticipates Claims 101, 105-111, 113-116, and 126-130, as these claims had recited a combination of ixabepilone and 5-fluorouracil (5-FU), and the '305 patent refers to combinations of cytotoxic agents including 5-FU at column 60, and to a method of making applicant's aza-epothilone B compound, ixabepilone, at Example 3 at column 96 etc. However, the combinations referred to at column 60 of '305 relate to combinations of "inventive compounds" (col. 59, line 61), and Example 3 of '305 purports only to reflect a new method of making the aza-epothilone B compound – it does not purport to represent that this compound was "inventive" (indeed, the compound had previously been published in, *inter alia*, WO 99/02514). Thus, the "inventive compounds" referred to at column 60 could not encompass Compound (1) herein, *i.e.*, ixabepilone.

Applicant further traverses the Section 102(e) rejection on the ground that for a reference to be anticipatory, the reference must be sufficiently specific that one skilled in

the art would "at once envisage" the claimed invention. *See* MPEP § 2132.02 Applicant submits the disclosure of '305 is too broad to satisfy this standard.

Notwithstanding the foregoing, and in the interest of expediting prosecution of this application, applicant has amended claims 101, 105-111, 113-116 and 126-30, to omit reference to 5-FU, such that these claims are directed to combinations of ixabepilone and capecitabine. Claim 112 has been canceled as duplicative of other claims. Accordingly, the rejection under Section 102(e) is rendered moot.

Rejections under Section 103

The Office Action rejects claims 102-04, 112, and 117-25 under Section 103(a) over Danishefsky ('305 patent) in view of Miwa, and claims 101-130 under Section 103(a), over Vite *et al.* (WO 99/02514, corresponding with US Pat. 6,605,599), in view of The Merck index. Given the amendments to claims 101, 105-111, 113-116 and 126-30, which omit reference to 5-FU, applicant will treat all rejections under Section 103(a) as applying herein to claims 101-111 and 113-130 (claim 112 having been canceled).

In considering obviousness, the Federal Circuit has established three essential standards for the USPTO to meet, as a minimum: (1) the prior art must contain *a suggestion or motivation* for modifying or combining the references; (2) the proposed modifications must have a reasonable expectation of success in the prior art; and (3) the references teach or suggest *all* claim limitations. *See In re Chu*, 66 F.3d 292, 36 USPQ2d 1089, 1094 (Fed. Cir. 1995); *In re Oetiker*, 977 F.2d 1443, 24 USPQ2d 1443, 1444-46 (Fed. Cir. 1992); and MPEP § 2143. The burden of satisfying these requirements rests with the PTO. *See* MPEP § 2142.

The Office action argues that one skilled in the field would have been motivated to combine capecitabine with ixabepilone, and would have had an expectation of success with this combination, in view of previous disclosures of 5-FU and other cancer agents, *e.g.,* as

disclosed in the '305 patent. Initially, as discussed above, applicant submits the '305 patent does not suggest a combination of 5-FU and ixabepilone.

However, even if a combination of 5-FU and another agent (*i.e,* ixabepilone) were suggested, this does not translate to an expectation by one skilled in the field that a combination of capecitabine with the other agent would be effective. This is because, as explained in the accompanying Lee Declaration, capecitabine is converted to 5-FU by the human thymidine Phosphorylase (ThdPase) enzyme in tumors. Thus, a compound may be highly effective in combinations with 5-FU but, if the same compound has an adverse or inconsequential effect on upregulation of dThdPase enzyme, an enhanced effect would not be expected in combinations with capecitabine as compared with combinations with 5-FU. To the contrary, a reduction in efficacy would likely be expected. Thus, the question whether one skilled in the field would be motivated to use a compound in combination with capecitabine should be based on the compound's effect on upregulation of the dThdPase enzyme, not whether the compound works with 5-FU. (*See, e.g.*, Lee Declaration, ¶ 8).

Here, as further explained in the accompanying Lee Declaration, preclinical work suggested that ixabepilone does *not* upregulate dThdPase levels (Lee Declaration ¶ 7-8). Thus, it was expected that ixabepilone would *not* have a synergistic effect in combination with capecitabine in preclinical tumor cell models. (Lee Declaration ¶ 8.)

Thus, applicant submits that based on the evidence of record, one of ordinary skill in the field would not have reasonably expected that combining capecitabine with ixabepilone would be successful in providing a pharmaceutical composition or method of treatment that is more effective than the combination of 5-FU and ixabepilone (*Cf.* Office Action at p. 5.) For this reason, a *prima facie* case is not established.

Additionally, even if the requirements for a *prima facie* obviousness case were satisfied, it is rebutted herein. In *Knoll v. Teva Pharm. USA*, 367 F.3d 1381 (Fed. Cir. 2004), the Federal Circuit held that unexpected beneficial results should be considered in

determining whether a combination of agents is obvious. In *Knoll*, at issue was a patent claim to a method of treating pain with a combination of hydrocodone (a/k/a Vicoden®) and ibuprofen. *Id.* at 1383. There was evidence in the case that the prior art had taught combining an opiod, such as hydrocodone, with various NSAIDs, such as ibuprofen. *Id.* at 1384. On this evidence, the district court had entered summary judgment on obviousness. However, the Federal Circuit reversed because there was no "evidence of prior art teaching or suggesting the enhanced biomedical effect of the combination of hydrocodone and ibuprofen." *Id.* The court further concluded that evidence of this enhanced effect should have been considered, even if gathered after the patent was granted. *Id.* at 1385.

Here, applicant has submitted the Declaration of the inventor, Francis Lee, explaining in detail preclinical data that was obtained via two confirmatory studies demonstrating that ixabepilone in combination with capecitabine produces greater than additive (*i.e.*, synergistic) effects and additionally, the reasons why Dr. Lee believed the advantageous effects to be surprising. (*See* Lee Declaration, ¶¶ 5-15) Detailed results in graphical and tabulated form are set forth at paragraphs 12 and 13.

Applicant submits that evidence of a surprisingly synergistic effect has now been sufficiently and convincingly presented to rebut any *prima facie* obviousness rejection (Cf. page 10 of the Office Action, finding a previously-submitted graph was not convincing apparently for the sole reason that applicant had not sufficiently explained the experimental evidence).

For the foregoing reasons, it is respectfully requested that the Section 103(a) rejections be withdrawn.

Obviousness-type double patenting

Claims 101 to 112 also stand rejected on grounds of obviousness-type double patenting in view of US Pat. 6,686,380 and 6,605,599, assigned to the present assignee.

On this point, applicant raises the same traversal as set forth above. The two referenced patents ('380 and '559), are cited for their disclosures of Compound (1) herein (*i.e.*, ixabepilone), and broad suggestions of potential uses with various other chemotherapeutic agents, namely, pyrimidine analogs. Regarding the reference to pyrimidine analogs, applicant notes that in *Knoll v. Teva Pharm. USA, supra,* the prior art taught a combination of an opiod, such as hydrocodone, with various NSAIDs, such as ibuprofen, but the obviousness ruling was reversed as there was no prior art teaching an *enhanced* effect with the *particular* claimed combination (*i.e.*, the species falling in the prior art generic disclosures). Likewise, here, there is no evidence in the prior art teachings that a greater than additive effect would be obtainable with the particular claimed combination, *i.e*, ixabepilone and capectiabine. Applicant thus respectfully requests that the obviouness double-patenting rejections be withdrawn.

IDS

Applicant brings to the Examiner's attention that an IDS is submitted herewith.

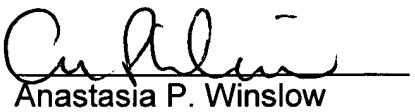
FEES

No fee is due for claim amendments. However, a fee is due for the one-month petition for extension of time and the accompanying IDS. The Commissioner is authorized to charge such fees to Deposit Account No. 19-3880 in the name of Bristol-Myers Squibb Company, as well as any additional fees that may be determined to be due.

SUMMARY

It is believed that all rejections of the claims have been fully addressed and that the instant claims are in condition for allowance. The Examiner is invited to contact the undersigned if it is believed a telephonic communication would expedite the prosecution of this application.

Respectfully submitted,



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